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ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

Medicina di precisione in oncologia pediatrica: dove siamo e dove stiamo andando

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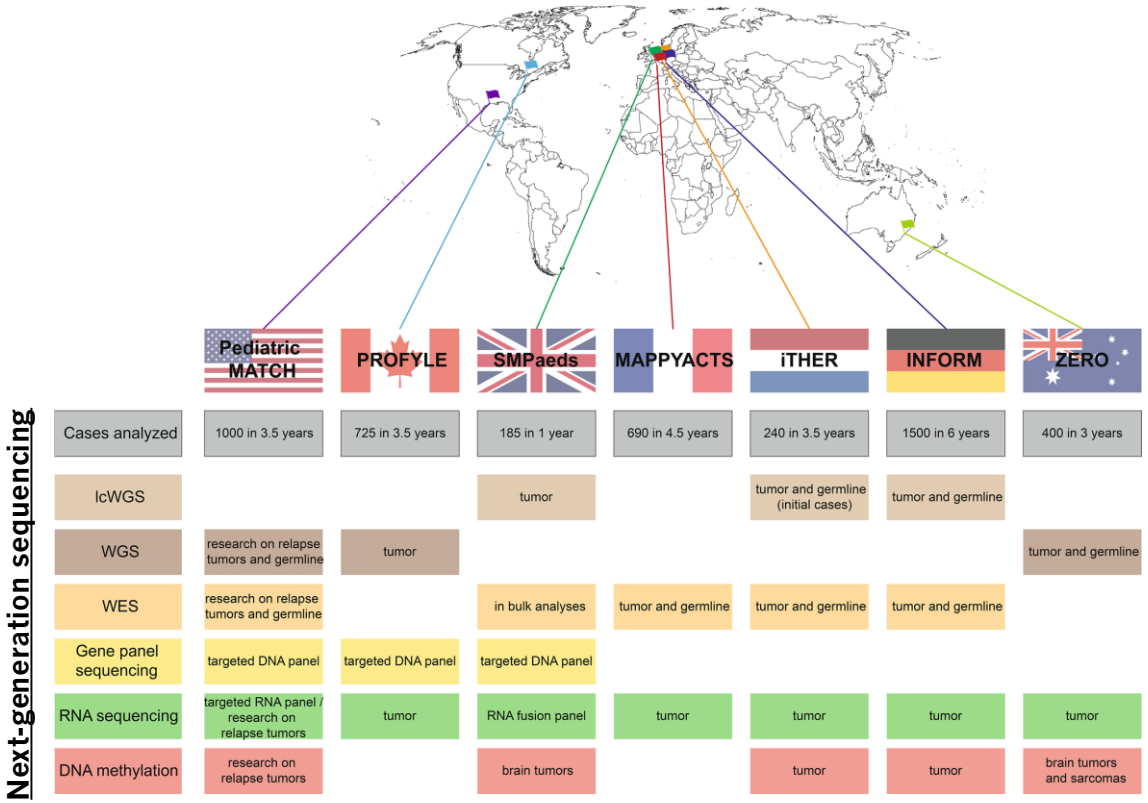
Milano, 22 e 23 maggio 2026

Medicina di Precisione in Oncologia Pediatrica

COSA STIAMO TROVANDO?

COSA CI ASPETTIAMO DI TROVARE?

International pediatric precision oncology platforms



- Identification of **tumor-specific alterations** which can serve as targets for **personalized therapy**.
- Mainly **focus on <u>relapsed</u>, <u>progressive</u> or very <u>high-risk</u> malignancies** due to the limited treatment options for these patients.

COSA STIAMO TROVANDO?

Cosa hanno scoperto queste ***piattaforme di medicina di precisione*** sui tumori pediatrici?

European Studies

MAPPYACTS

RESEARCH ARTICLES | MAY 02 2022

The European MAPPYACTS Trial: Precision Medicine Program in Pediatric and Adolescent Patients with Recurrent Malignancies

Pablo Berlanga; Gaelle Pierron; Ludovic Lacroix; Mathieu Chicard; Tiphaine Adam de Beaumais; Antonin Marchais; Anne C. Harttrampf; Yasmine Iddir; Alicia Larive; Aroa Soriano Fernandez; Imene Hezam; Cecile Chevassus; Virginie Bernard; Sophie Cotteret; Jean-Yves Scoazec; Arnaud Gauthier; Samuel Abbou; Nadege Corradini; Nicolas André; Isabelle Aerts; Estelle Thebaud; Michela Casanova; Cormac Owens; Raquel Hladun-Alvaro; Stefan Michiels; Olivier Delattre; Gilles Vassal; Gudrun Schleiermacher; Birgit Geoerger

- *Cases: 689 in 4.5 years*
- *WES and RNAseq*

Cancer Discov (2022) 12 (5): 1266–1281.

INFORM

RESEARCH ARTICLES | NOVEMBER 01 2021

The Pediatric Precision Oncology INFORM Registry: Clinical Outcome and Benefit for Patients with Very High-Evidence Targets

Cornelis M. van Tilburg; Elke Pfaff; Kristian W. Pajtler; Karin P.S. Langenberg; Petra Fiesel; Barbara C. Jones; Gnana Prakash Balasubramanian; Sebastian Stark; Pascal D. Johann; Mirjam Blattner-Johnson; Kathrin Schramm; Nicola Dikow; Steffen Hirsch; Christian Sutter; Kerstin Grund; Arend von Stackelberg; Andreas E. Kulozik; Andrej Lissat; Arndt Borkhardt; Roland Meisel; Dirk Reinhardt; Jan-Henning Klusmann; Gudrun Fleischhack; Stephan Tippelt; Dietrich von Schweinitz; Irene Schmid; Christof M. Kramm; André O. von Bueren; Gabriele Calaminus; Peter Vorwerk; Norbert Graf; Frank Westermann; Matthias Fischer; Angelika Eggert; Birgit Burkhardt; Wilhelm Wößmann; Michaela Nathrath; Stefanie Hecker-Nolting; Michael C. Frühwald; Dominik T. Schneider; Ines B. Brecht; Petra Ketteler; Simone Fulda; Ewa Koscielniak; Michael T. Meister; Monika Scheer; Simone Hettmer; Matthias Schwab; Roman Tremmel; Ingrid Øra; Caroline Hutter; Nicolas U. Gerber; Olli Lohi; Bernarda Kazanowska; Antonis Kattamis; Maria Filippidou; Bianca Goemans; C. Michel Zwaan; Till Milde; Natalie Jäger; Stephan Wolf; David Reuss; Felix Sahm; Andreas von Deimling; Uta Dirksen; Angelika Freitag; Ruth Witt; Peter Lichter; Annette Kopp-Schneider; David T.W. Jones; Jan J. Molenaar; David Capper; Stefan M. Pfister; Olaf Witt

- *Cases: 1500 in 6 years*
- *WES, RNAseq and lcWGS*

Cancer Discov (2021) 11 (11): 2764–2779.

Definizione "**Potentially targetable genetic alteration**"

- ALTERAZIONE GENETICA E' CONSIDERATA **POTENZIALMENTE TRATTABILE** PERCHÉ:

1. **Esiste un farmaco approvato** che agisce direttamente sull'alterazione genetica
2. **Esiste un farmaco sperimentale** (in fase preclinica o clinica) che agisce direttamente sull'alterazione genetica.

- ALTERAZIONE GENETICA **ALTAMENTE PRIORITARIA**

1. **MAPPYACTS, Ready for clinical use**: esiste una corrispondenza nota tra **l'alterazione** e un farmaco con un'attività anti-tumorale (>**30% tasso di risposta obiettiva,** ORR) nei trial clinici (stesso tumore o simile)
2. **INFORM, Very High Priority**: gene direttamente bersagliabile noto per essere un driver in una specifica entità tumorale, con **mutazione puntiforme driver confermata** o **fusione attivante confermata**/molto **probabile**.

Comparison of two pediatric precision oncology studies

Overall cohort-level findings on targetable alterations and matched targeted treatment

MAPPYACTS

632 sequenced total patients

Sequenced total patients	632	
At least one targetable alteration	69% 436/632	
At least one ready-for-use alteration	7% 44/632	
Received targeted matched treatment	24% 107/436 among patients with a targetable alteration	17% 107/632 among all sequenced patients

INFORM

519 sequenced tumors

Sequenced tumors	519
At least one targetable alteration *very high / high / moderate priority*	43% 225/519
At least one very high priority alteration	8% 42/519
Received targeted matched treatment	65% 147/225 | 29.3% 147/519

- Targetable alterations were more frequent in Study 1: **69%** vs **43%**.
- Highest-priority actionable alterations were similar: **7%** in Study 1 vs **8%** in Study 2.*
- Matched targeted treatment across the full cohort was higher in Study 2: **29.3%** vs **17%**.

Dati sul trattamento su tutti i pazienti

MAPPYACTS

- Valutazione complessiva (109 pazienti valutabili):
  - **Risposta parziale (PR):** 18 pazienti (**17%**; IC 95%: 10%-25%) ORR
  - **Malattia stabile (SD):**
  - **Controllo della malat**
    pazienti; IC 95%: 32%
  - **Durata mediana del t**
    malattia controllata):
    697 giorni)
- **Alterazioni "** *ready for use* **" (13 pazienti):**
  - **ORR** (>30% tasso di risposta obiettiva) **: 38% (5/13**; IC 95%: 18%-65%)
  - 💊 Tutti trattati con farmaci singoli

Benefici chiari per i pazienti con target ad alta priorità trattati con terapie mirate

INFORM

- **42** pazienti con target molecolare ad **alta priorità (very high)**:
- **20** pazienti **hanno ricevuto** un trattamento mirato:
  - **PFS mediana: 294 giorni** (IC 95%: 99–NA)
  - %: 165–NA)
- ttamento mirato**:**
  - **P = 0.011**)
  - P = 0.32)
- a priorità **non ha ricevuto terapia mirata**.
  - Progressione rapida della malattia.
  - Mancanza di disponibilità del farmaco.
  - Rifiuto del paziente/famiglia.
  - Costi non coperti dalle assicurazioni.

Results of PREME: Precision Medicine for Neuroblastoma

18 patients

66% of samples had alterations potentially targetable

4/18 (22%) patients patients recieved a molecular targeted therapy

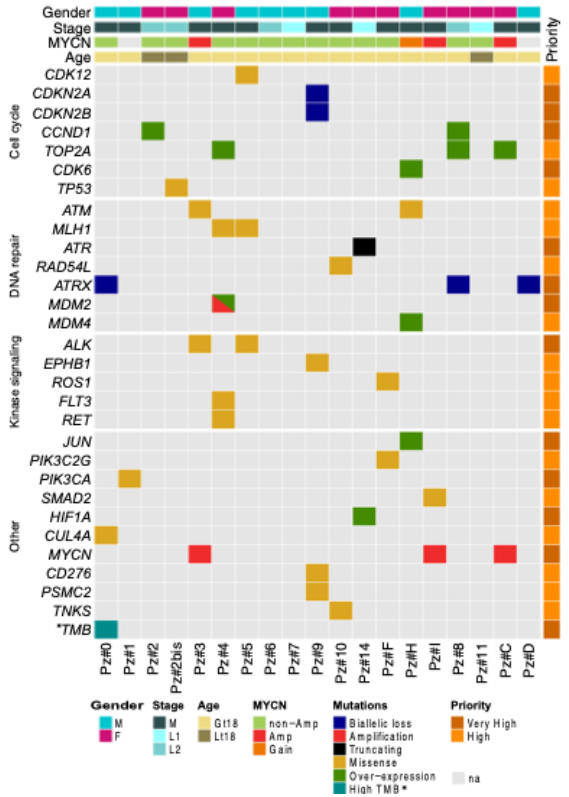
12% genetic predisposition

Capasso *et al.*
Journal of Translational Medicine (2024) 22:151
https://doi.org/10.1186/s12967-024-04954-w

Journal of Translational Medicine

RESEARCH Open Access

From the identification of actionable molecular targets to the generation of faithful neuroblastoma patient-derived preclinical models



Cosa ci aspettiamo di trovare?

- Alterazioni molecolari che sono bersagli terapeutici validati da studi prospettici specifici per la tipologia di tumore da trattare
- FDA-approved *alterations/drugs* including all tumors (OncoKB):
  - 55 targeted genes, 38 cancer types
  - 189 clinical applications
- FDA-approved alterations/drugs for **pediatric solid tumors**
  - 7/55 (**13%**) targeted genes, 6 cancer types
  - 17/189 **(9%)** clinical applications

FDA approved molecular targets in pediatrics marzo 2025

Cancer Type	Pediatric Tumor Category	Gene	Drugs
B-Lymphoblastic Leukemia/Lymphoma	Leukemia and Lymphoma	ABL1 (BCR-ABL1 Fusion, T315I), KMT2A (Fusions)	Dasatinib, Imatinib, Ponatinib, Revumenib
Acute Myeloid Leukemia (AML)	Leukemia and Lymphoma	KMT2A (Fusions)	Revumenib
Acute Leukemias of Ambiguous Lineage	Leukemia and Lymphoma	KMT2A (Fusions)	Revumenib
Anaplastic Large-Cell Lymphoma ALK Positive	Leukemia and Lymphoma	ALK (Fusions)	Crizotinib
Low-Grade Glioma, NOS	Central nervous system	BRAF (Fusions, V600E)	Tovorafenib, Dabrafenib + Trametinib
Encapsulated Glioma	Central nervous system	TSC1 (Oncogenic Mutations), TSC2 (Oncogenic Mutations)	Everolimus
Oligodendroglioma, Astrocytoma	Central nervous system	IDH1 (5 SNVs), IDH2 (4 SNVs)	Vorasidenib
Inflammatory Myofibroblastic Tumor	Sarcomas	ALK (Fusions)	Crizotinib
Epithelioid Sarcoma	Sarcomas	SMARCB1 (Deletion)	Tazemetostat

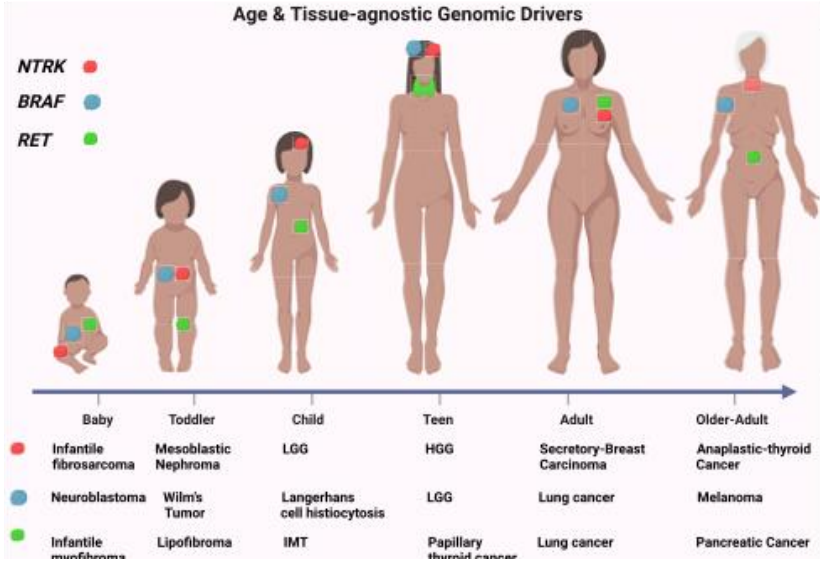
FDA-approved tissue-agnostic therapies

Alterazioni molecolari che sono bersagli teraupetici in pazienti con diversa età e con diversi tumori

microsatellite instability high

tumor mutational burden

Target	Drug	Children included	Year approved	Cancers included	Comments
Molecular biomarker-based tissue-agnostic approvals					
MSI-H/deficient MMR genes	Pembrolizumab (anti-PD1)	**Children included No age restriction**	2017	Solid tumors	Tissue-agnostic Solid tumors
NTRK fusions	NTRK inhibitor larotrectinib	**Children included No age restriction**	2018	Tissue-agnostic Solid tumors	Tissue-agnostic
NTRK fusions	Entrectinib (NTRK inhibitor)	**Children ≥12 years old**	2019	Tissue-agnostic Solid tumors	Tissue-agnostic
NTRK fusions	Repotrectinib (NTRK inhibitor)	**Children ≥12 years old**	2024	Tissue-agnostic Solid tumors	Tissue-agnostic Solid tumors
TMB-high (≥10 mutations/mb)	Pembrolizumab (anti-PD1)	**Children included No age restriction**	2020	Solid tumors	Tissue-agnostic
BRAF V600E mutations	Dabrafenib (B-Raf inhibitor) plus trametinib (MEK inhibitor)	**Children ≥ 6 years old**	2022	Solid tumors	Tissue-agnostic Colorectal cancer excluded.
RET fusions	Selpercatinib	**Children >2 years and above**	2024	Solid tumors	Tissue-agnostic



NTRK1-2-3 fusions, RET fusions, BRAF V600 mutations

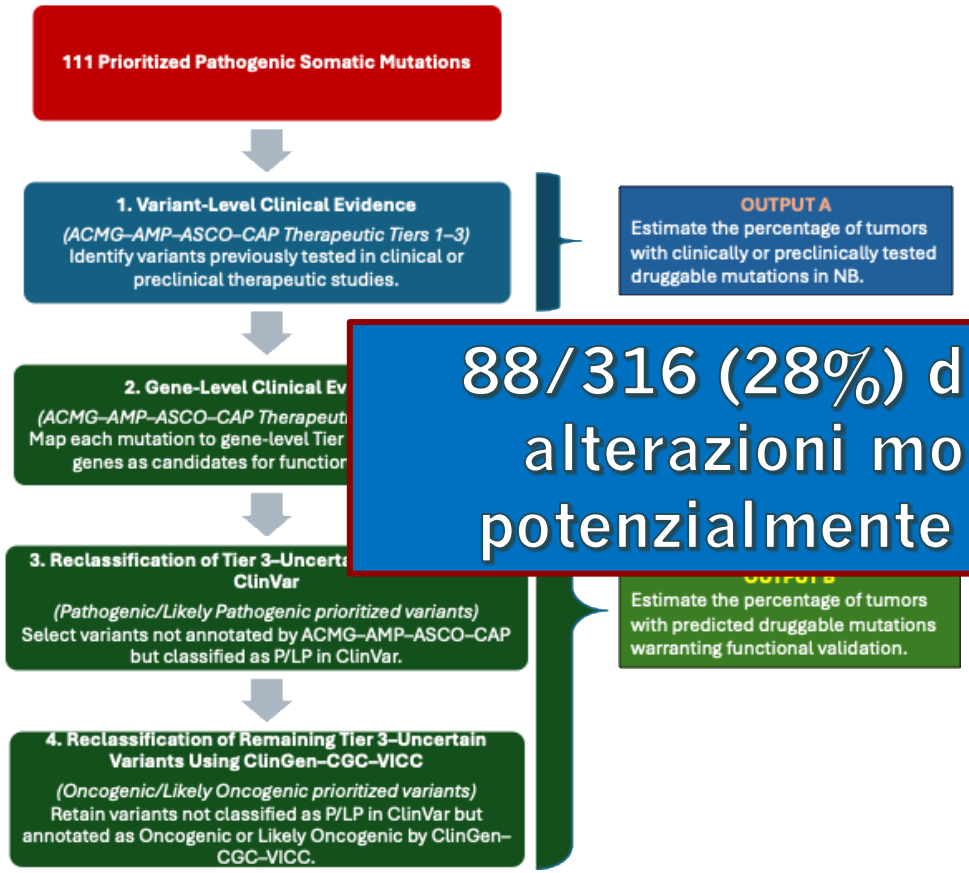
9/55 (16%) approved target genes + High MSI and TMB

Cancer Cell 42, September 9, 2024

Somatic druggable relevant point mutations in 316 WGS from neuroblastoma

- 566 cancer genes
- Mutations with:
  functional impact predictions
  ClinVar annotation

D



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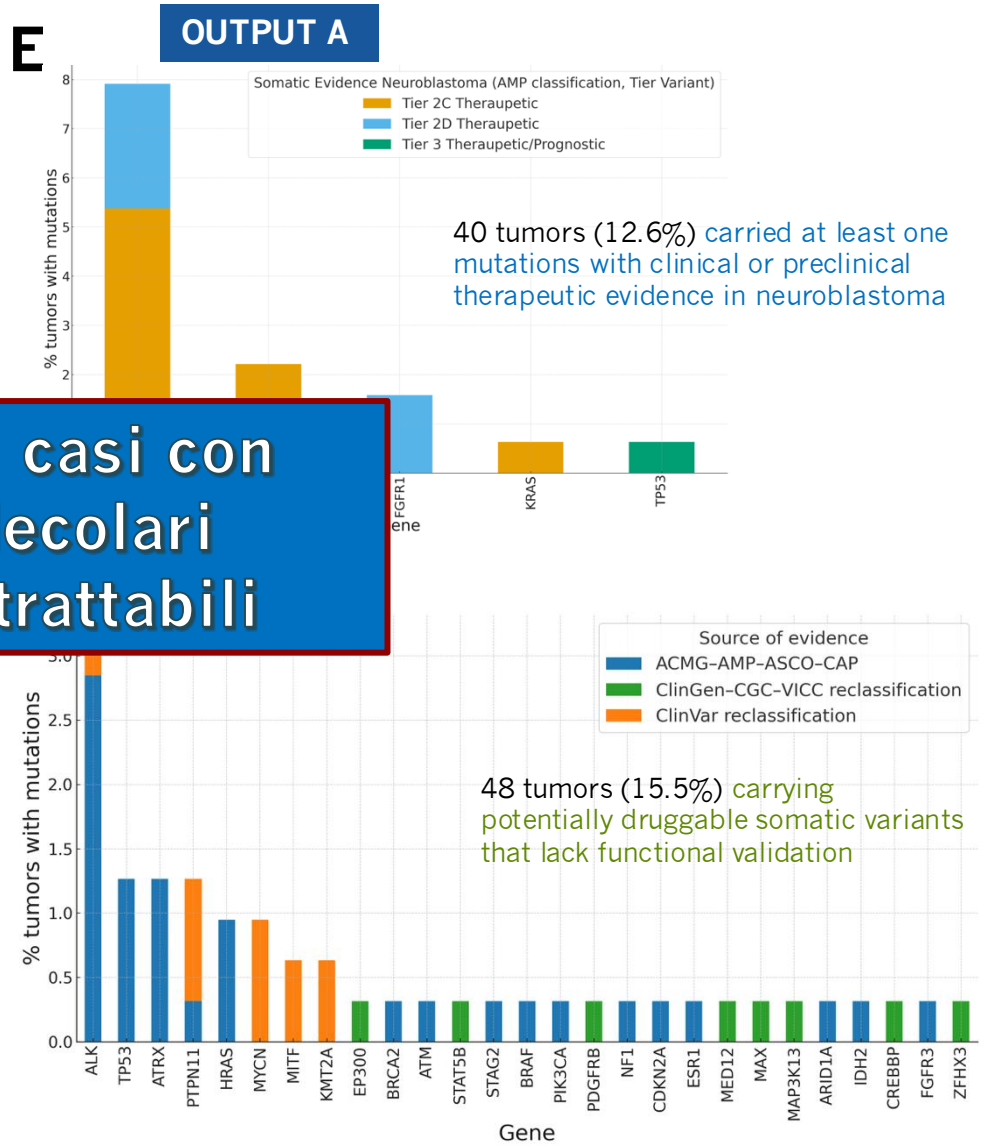


88/316 (28%) di casi con alterazioni molecolari potenzialmente trattabili

D'Alterio et al. submitted *Genes & Diseases*

How to increase the FDA approved alteractions/drugs for pediatric tumors?

Intensify 3 main actions

Increase knowledge of genomics and biology of diatric tumors

- **1.Novel Tumor-agnostic and -specific Molecular Alterations**
- **2.Identifying Germline Druggable Mutations**
- **3.Tumor heterogeneity**

Assess the interaction between molecular alterations and drugs

- **1. in vitro preclinical studies**
- **2. in vivo preclinical studies**

Assess clinical utility of the targeted therapy

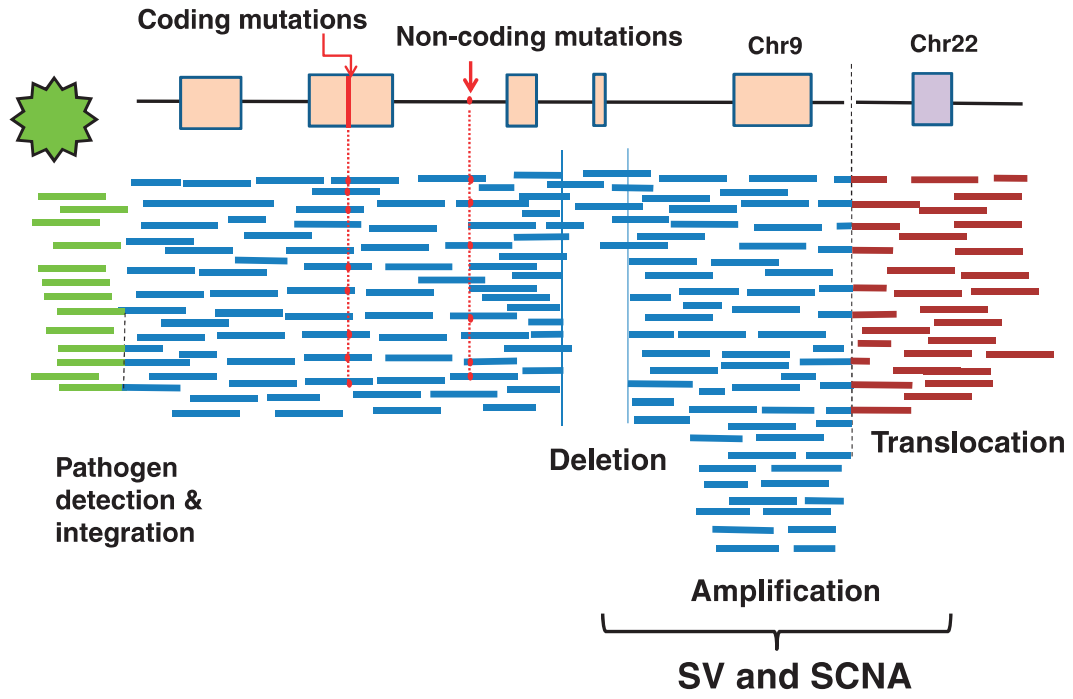
- **1. Access to drugs**
- **2. Developing Clinical Protocols**

1. Novel molecular alterations (tumor specific or agnostic)

Whole Genome Sequencing (WGS)

- WGS can detect non-coding mutations, SVs (structural variants) including SCNAs (somatic copy number alterations) and translocations,
- Combining WGS and RNA sequencing

  Alternative isoform and gene fusion



Target vs WES vs WGS

- **Identification of Actionable Variants:**
  - **Targeted Gene Panel:** 32% of participants
  - **WGS:** 62% of participants
  - **After Integrating RNAseq Analysis:** 96% of participants
- **Clinical Impact of Molecularly Informed Therapies:**
  - **32 therapies were pursued in 28 participants.**
  - **54% of patients achieved clinical benefit** (defined as objective response or stable disease for ≥6 months).

nature medicine
Accepted: 8 May 2024
Article
https://doi.org/10.1038/s41591-024-03056-w

Benefits for children with suspected cancer from routine whole-genome sequencing

nature communications
Accepted: 29 April 2024
Article
https://doi.org/10.1038/s41467-024-48363-5

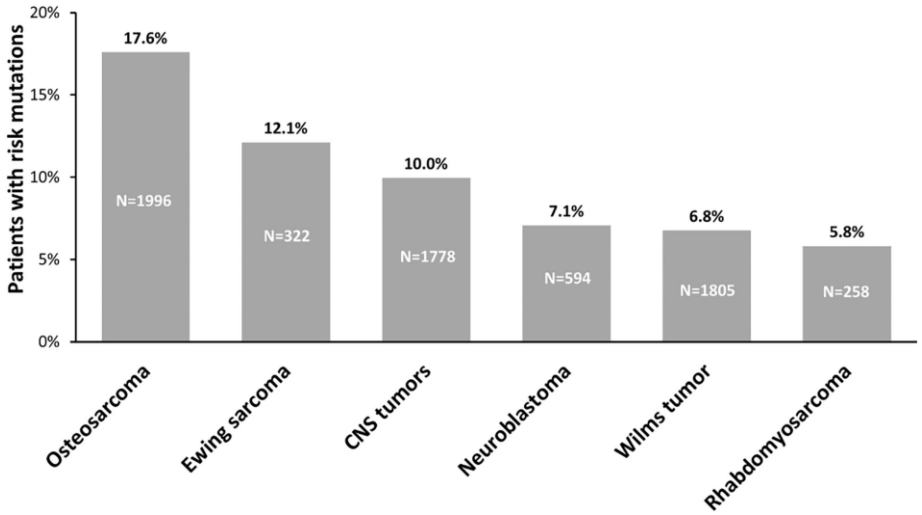
Whole genome and transcriptome integrated analyses guide clinical care of pediatric poor prognosis cancers

nature genetics
Accepted: 1 May 2024
Article
https://doi.org/10.1038/s41588-024-01785-9

Analysis of 10,478 cancer genomes identifies candidate driver genes and opportunities for precision oncology

2) Identifying Germline Druggable Mutations

6-18% pediatric cancers carry at least one rare cancer predisposition mutation



Examples of inherited alterations that may guide targeted treatment

1 Homologous recombination repair (HRR) genes

- **Genes:** *BRCA1/2*, *ATM*, Fanconi anaemia genes, *CHEK2*, *BRIP1*, *PALB2*, *RAD51C*, and others
- **Biologic rationale:** impaired homologous recombination repair makes tumor cells less able to repair DNA damage
- **Potential sensitivity:** **platinum-containing agents** and PARP inhibitors (e.g., **Olaparib**)
- **Clinical note:** **Olaparib** is standard of care in ovarian cancer with germline *BRCA1/2* mutations
- Potential benefit also reported in breast, prostate, and pancreatic cancers with germline *BRCA1/2* or *ATM* mutations
- **Selected studies:** NCT02032823, NCT02987543, NCT02184195

2 *ALK* germline variants

- **Gain-of-function variants:** R1275Q, R1060H, *I1183T*, *L1204F*, *R1231Q*, *I1250T*
- Preclinical evidence suggests sensitivity to **crizotinib**; some variants may also predict resistance
- **Reference:** *Cancer Cell* 26, 682-694 (2014)
- **Clinical signal:** in phase I study NCT00939770, 2 patients with germline *ALK* variants were treated with **crizotinib**
- **Outcome:** one patient had marked symptom improvement and one achieved a complete response

3 *NF1* germline mutations

RAS → RAF → MEK → ERK

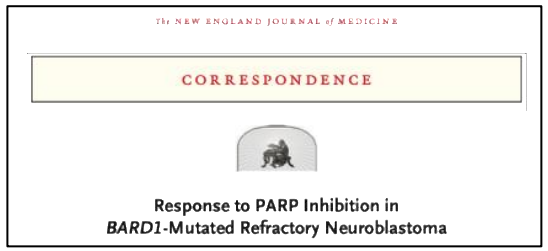
- Loss of *NF1* activity increases RAS pathway signaling
- **Potential sensitivity:** **selumetinib** (MEK inhibitor)
- Patients with germline *NF1* mutations may benefit from MEK pathway inhibition
- **Selected studies:** NCT03326388, NCT01089101

4 Mismatch repair (MMR) deficiency

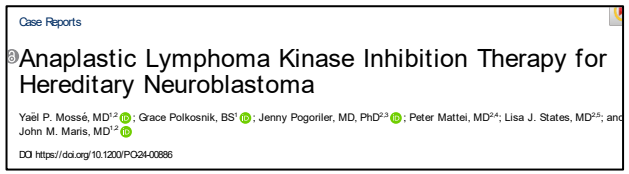
- **Genes:** *MSH2*, *MLH1*, *PMS2*, *MSH6*, *POLE*, and others
- Defective mismatch repair can lead to high mutational burden and increased immunogenicity
- **Potential sensitivity:** **immune-checkpoint inhibition (ICI)**
- **Rationale:** these tumors may express key immunomodulators and respond better to checkpoint blockade

Capasso et al. Frontiers in Oncology, 2020

Germline Variants may be Actionable Therapeutic Targets of PARP and ALK inhibitors: *three successful cases*



- **Patient:** Metastatic high-risk neuroblastoma, refractory to standard therapy
- **Genetics:** Pathogenic germline *BARD1* loss-of-function variant (loss of DNA repair function)
- **Treatment:** PARP inhibition (talazoparib + irinotecan)
- **Outcome:** Early complete response and durable remission (32 months)



Patient 1 (girl, 6 months):
Diagnosis: Stage IV neuroblastoma, bilateral adrenal tumors

Refractory to standard therapy

Germline **mutation ALK R1275Q**

Relapse → **crizotinib** therapy → complete response

Therapy maintained 5 years → now in **remission for 8 years**

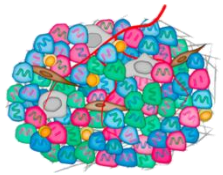
Patient 2 (mother, 36 years old):
Silent carrier of the **ALK R1275Q mutation**. No surveillance

Diagnosis: bilateral neuroblastoma during second pregnancy

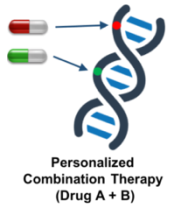
Treatment: crizotinib → replaced with **alectinib** (did not tolerate crizotinib)

Bilateral surgery + therapy → complete remission **maintained 28 months**

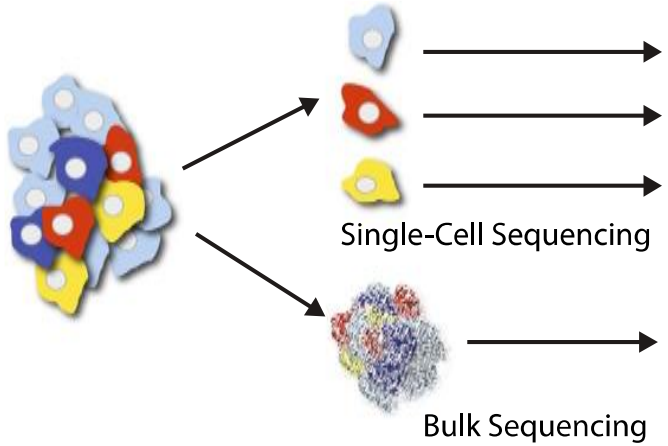
3) Tumor heterogeneity



- **Eterogeneità del tumore:** La diversità e l'evoluzione del tumore nel tempo evolve sotto trattamento (*meccanismi di resistenza*).



- **Combinazioni terapeutiche:** Utilizzo di terapie mirate con *chemio o con altri agenti mirati* per ridurre effetti collaterali ed evitare resistenze.



Single cell sequencing: measurements of biological contributions of each cell to healthy or diseased tissues

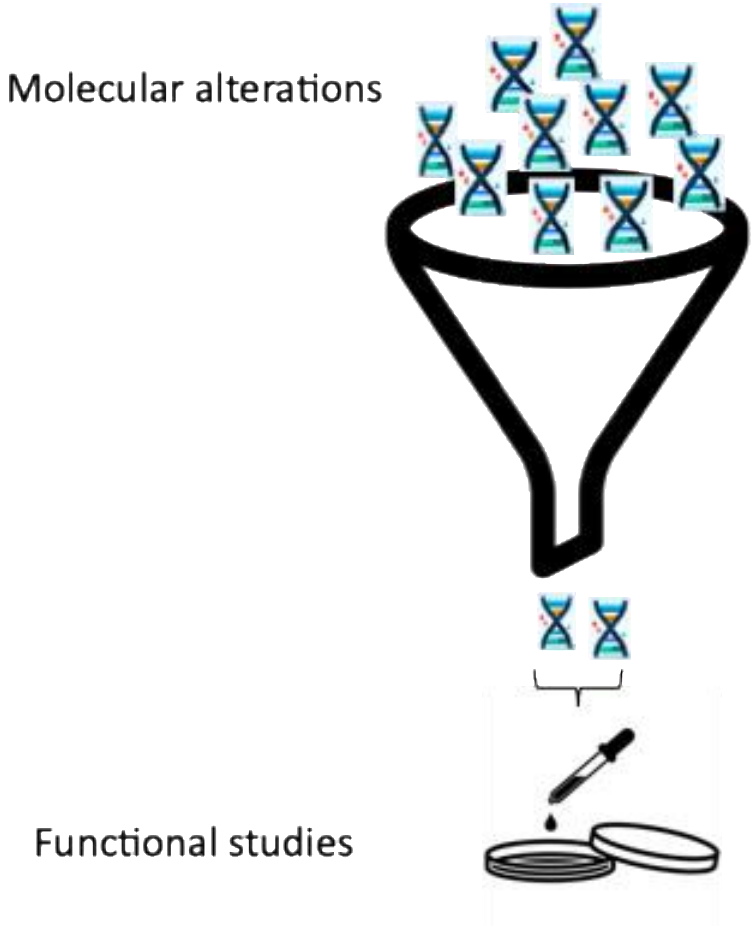
Bulk sequencing: reflects an average signal of mixed cells

Advantages: to detect mRNA expression, epigenomics changes, or genomic variants that can be lost by bulk sequencing.

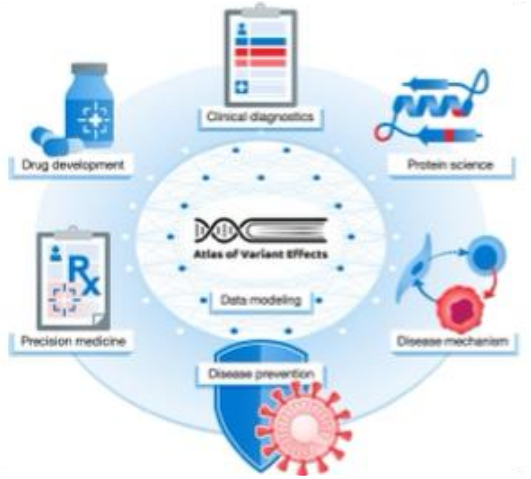
Assess the interaction between molecular alterations and drugs

1) In vitro preclinical studies

Comprendere le implicazioni funzionali e cliniche delle alterazioni genomiche

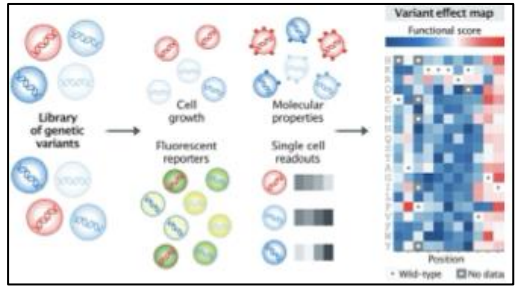


Gene-drug interaction



Gruppo collaborativo internazionale per realizzare Atlante degli Effetti delle Varianti

Genome Biology volume 24, Article number: 147 (2023)



Multiplexed assays of variant effect (MAVEs)

Assess the interaction between molecular alterations and drugs

2) In vivo preclinical studies

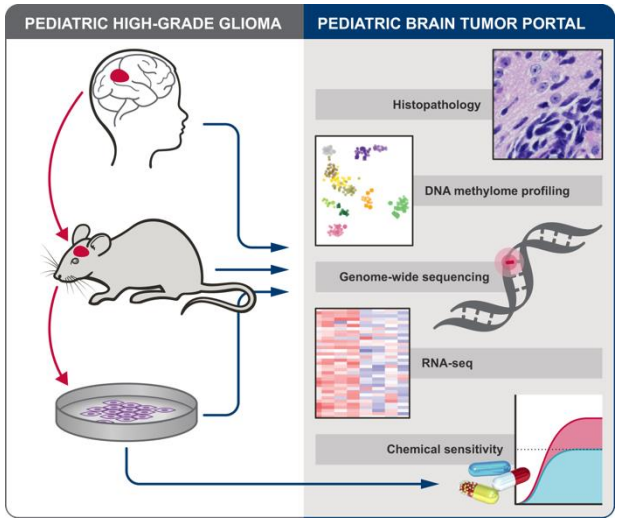
Need of Models that reflect human cancer biology and genetics.

Review Article | Published: 23 September 2022

Towards precision oncology with patient-derived xenografts

Eugenia R. Zanella, Elena Grassi & Livio Trusolino

Nature Reviews Clinical Oncology **19**, 719–732 (2022) | Cite this article



Capasso et al.
Journal of Translational Medicine (2024) 22:151
https://doi.org/10.1186/s12967-024-04954-w

Journal of Translational Medicine

RESEARCH Open Access

From the identification of actionable molecular targets to the generation of faithful neuroblastoma patient-derived preclinical models

Article | Open access | Published: 18 September 2023

A biobank of pediatric patient-derived-xenograft models in cancer precision medicine trial MAPPYACTS for relapsed and refractory tumors

Assess clinical utility of the targeted therapy

1) Developing Clinical Protocols
2) Access to drug

1. Problemi nei trial pediatrici:

- **Ritardi nei trial pediatrici:** Gli studi clinilci nei bambini vengono spesso condotti solo su farmaci già efficaci nei tumori adulti.
- **Numero limitato di pazienti:** Nei trial pediatrici, soprattutto quelli basati su biomarcatori, il numero di pazienti idonei è molto ridotto.
- Protocolli clinici con **design statistici flessibili**.
- Utilizzo di **nuovi farmaci** anche in **fasi iniziali della malattia**

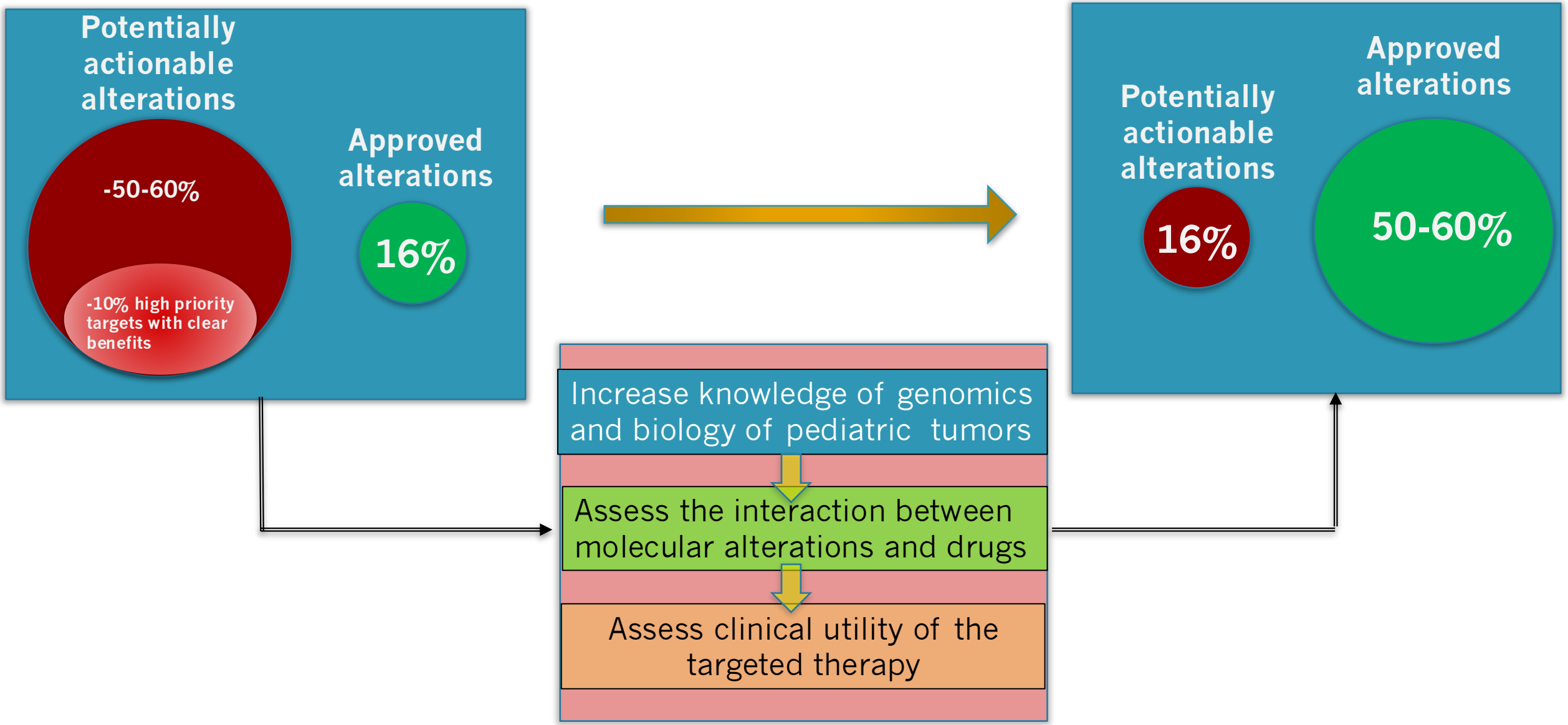
2. Tipologie di trial innovativi:

- **Basket trial:** Coinvolgono pazienti con tumori diversi ma con alterazioni genetiche specifiche (es. MATCH, AcSé-ESMART).
- **Umbrella trial:** Pazienti con lo stesso tipo di tumore vengono assegnati a trattamenti mirati in base a specifiche alterazioni molecolari.
- **Condivisione e armonizzazione dei dati** clinici, dati molecolari e metodi di classificazione delle varianti

3. Ostacoli regolatori e industriali:

- **Bassa disponibilità di farmaci e interesse aziendale:** La legge RACE per bambini (FDA, 2020) obbliga le aziende a testare nuovi farmaci oncologici pediatrici quando il meccanismo d'azione è rilevante per i bambini.

Conclusions

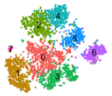


Italian Multicentre Project

Advanced Genomic Strategies to Uncover Clinically Actionable Molecular Alterations in Neuroblastoma

AlterAction (2025-2027)

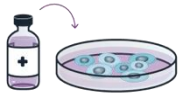
- **Long-reads sequencing**



- **Single cell RNA sequencing**

- **WES per** Clinically Relevant Rare Onco-predisposing Variants

- **Massively Parallel Functional Characterization** of SNVs in a Gene Often Mutated at the Somatic Level



- **Detailed Functional Analyses** of the Genetic Variants Associated with Familial NB.

Improve Personalized Medicine

- Identificazione di Target Terapeutici
- Personalizzazione della terapia
- Riduzione della Resistenza ai Farmaci
- Prognosi e Predizione della Risposta al Trattamento
- Sviluppo di Test Diagnostici e Predittivi

OPEN ASSOCIAZIONE ONCOLOGIA PEDIATRICA E NEUROBLASTOMA ONLUS

FONDAZIONE ITALIANA PER LA LOTTA AL NEUROBLASTOMA ETS

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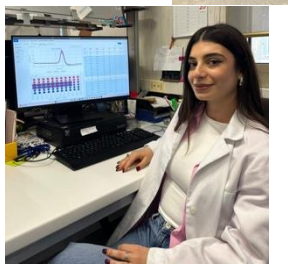

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GRAZIE!!

Conclusion and outlook

- **1. Advances Through Clinical Sequencing Initiatives**
- Deeper biological insights into childhood tumors.
- **Examples of success**: Sustained responses with matched target and treatment: **BRAF V600E**, **NTRK fusion, RET fusion**, **ALK mutations, IDH1 and IDH2 mutations**
- **Germline variation** as therapeutic target and markers of drug toxicity
- **2. Additional Profiling Methods**
- **Combined WGS and RNAseq**
- **Long reads sequencing**: new SVs
- **Single-cell genomics**: Explores tumor heterogeneity for personalized treatments and understand the resistance mechanisms
- **Multiplexed assays of variant effect (MAVEs):** discover the effects of genetic variants
- **Liquid biopsy monitoring**: Tracks mutational profiles during treatment.
- **Proteomic analysis**: Identifies protein-level changes for treatment targeting.

Conclusion and outlook

- **3. Challenges**
- **Clinical trial design**:
  - Needs to be faster and more flexible.
  - Allows testing of targeted agents in smaller subsets of patients.
- **Combination therapies**: Improve outcomes through synergistic treatments.
- **Pediatric access**:
  - Accelerate the development of new drug.
  - Ensures logical and effective treatment options.

GRAZIE!!

- 519 sequenced **tumors**
  - 225/519 (43%) patients with at **least one targetable alteration** (*very high, high, or moderate priority score*)
  - 42/519 (8%) patients with at **least one very high priority alteration**
  - 147/519 (29.3%) patients recieved a **targeted matched treatment**

Potentially targetable genetic alterations in Solid Tumors

MAPPYACTS

- 632 sequenced **total patients**:
  - 436 /632 (69%) patients with at least **one targetable alteration**
  - 44/436 (10%) patients with at least **ready for use alteration**
  - 107/436 (24%) of patients recieved a **targeted matched treatment**
  - 107/632 (17%) of all patients recieved a targeted matched treatment

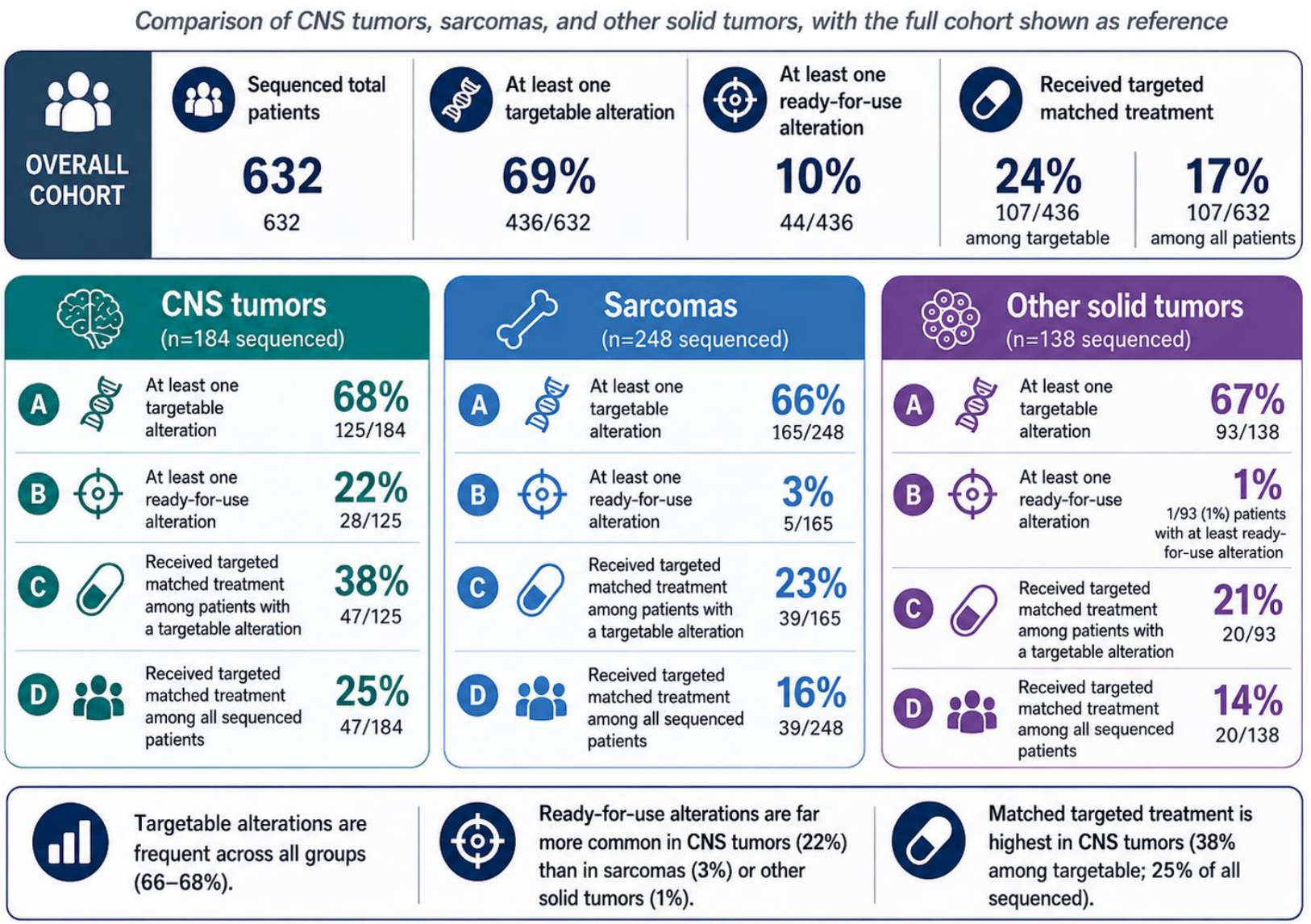
- 184 sequenced **CNS**:
  - 125 /184 (68%) patients with at least **one targetable alteration**
  - 28/125 (22%) patients with at least **ready for use alteration**
  - 47/125 (38%) of patients recieved a **targeted matched treatment**
  - 47/184 (25%) of all patients recieved a targeted matched treatment

- 248 sequenced **sarcomas**:
  - 165 /248 (66%) patients with at least **one targetable alteration**
  - 5/165 (3%) patients with at least **ready for use alteration**
  - 39/165 (23%) of patients recieved a **targeted matched treatment**
  - 39/248 (16%) of all patients recieved a targeted matched treatment

- 138 other sequenced **solid tumors**:
  - 93/138 (67%) patients with at **least one targetable alteration**
  - 1/93 (1%) patients with at least **ready for use alteration**
  - 20/93 (21%) patients recieved a **targted matched treatment**
  - 20/138 (14%) of all patients recieved a targted matched treatment

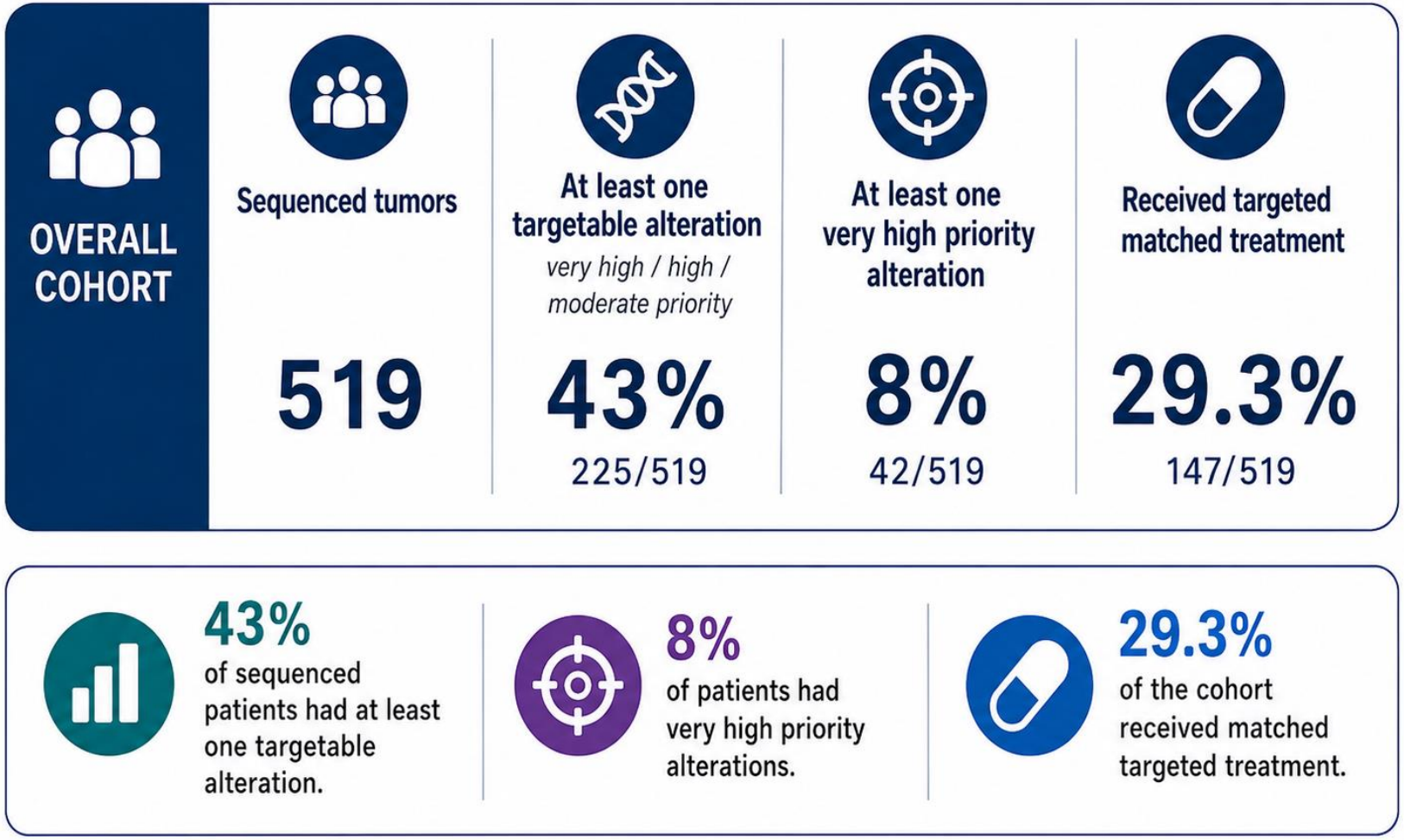
Potentially targetable genetic alterations across tumor groups

MAPPYACTS



Potentially targetable genetic alterations

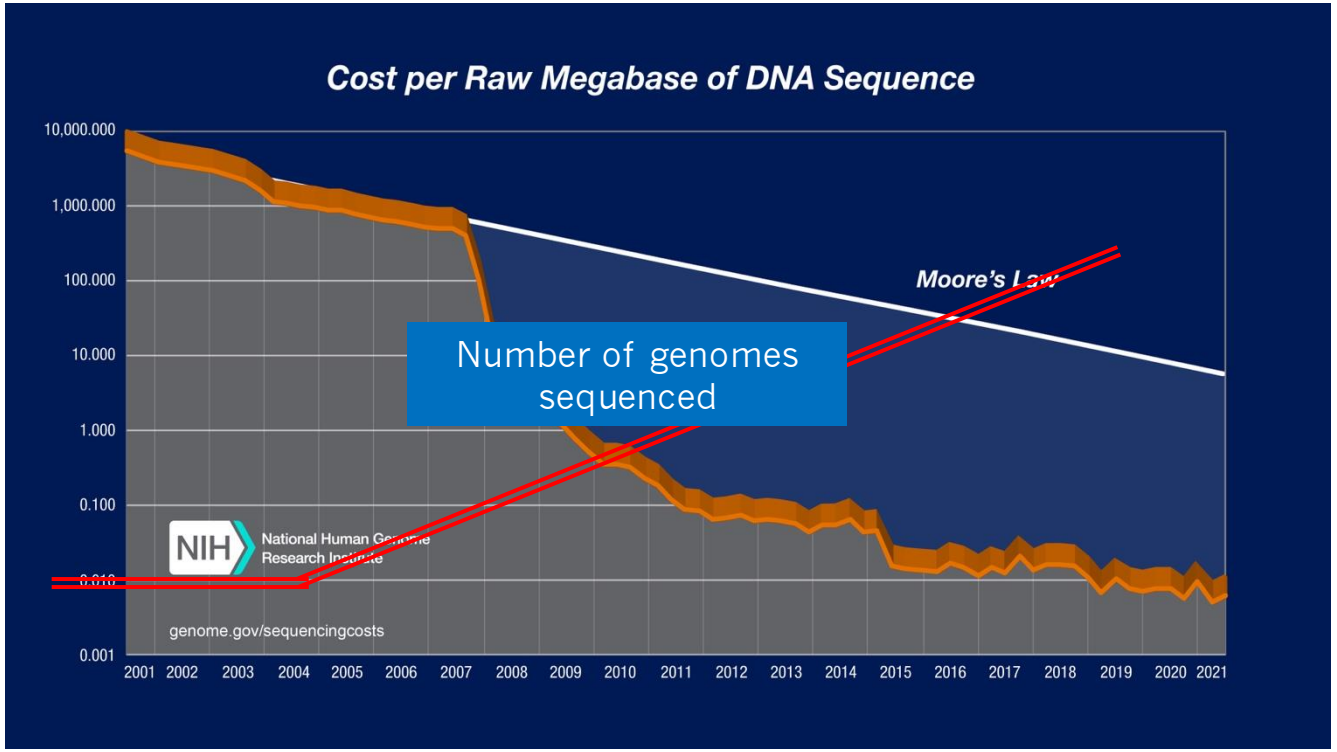
INFORM



2007: Genomic Revolution

Next generation sequencing

- The ability to process millions of sequence reads in parallel
- It requires only one or two instruments runs to complete an experiments



The landscape of genomic alterations across childhood cancers

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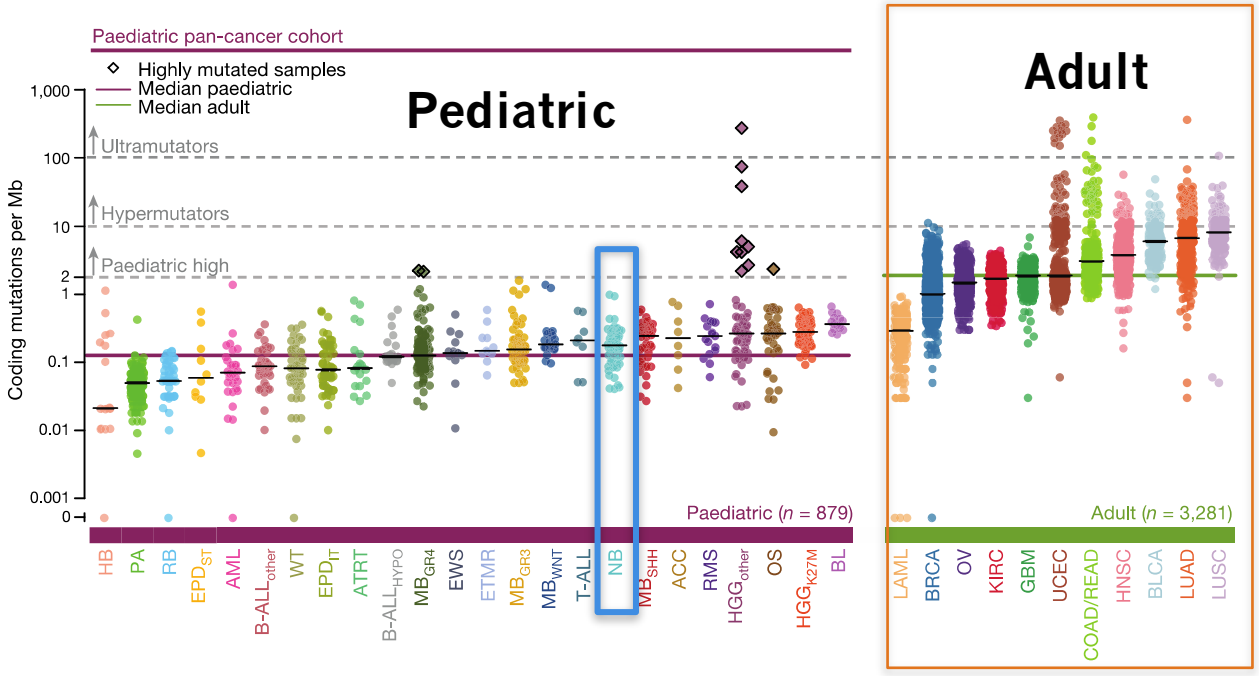
Next generation sequencing

961 tumours from children, adolescents, and young adults comprising **24 distinct molecular types of cancer**



1. **Rate** of pathogenic **mutations** in pediatric cancers is **lower** than that of adult cancers
2. **50%** of pediatric neoplasms has potentially **druggable events**
3. **10%** of the children carries **predisposing germline variant**

Translational genomics findings in pediatric oncology

Sviluppare terapie che trattano il cancro sulla base di alterazioni genomiche del tumore del paziente